Lipid A and Related Compounds. XXVII.[1] An Efficient Synthesis of D-Galactosamine-4-phosphate Analogs of Lipid A *via* a Novel Key Intermediate

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A new methodology for chemical differentiation of one amino and four hydroxyl groups of D-galactosamine derivatives and its application for the synthesis of D-galactosamine-4-phosphate analogs of lipid A are described. Preliminary examination of biological activity revealed that the synthetic monosaccharides show mitogenic activity.

Keywords D-galactosamine-4-phosphate; lipid A analog; mitogenic activity; D-galactosamine derivative; chemical differentiation; key intermediate

Lipid A of gram-negative bacterial lipopolysaccharides (LPS) is of considerable pharmacological interest, because it is responsible for the expression of many biological activities of LPS, *e.g.*, endotoxicity, adjuvanticity, antitumor activity and so on.[2] Lipid A consists of a D-glucosaminyl-$\beta(1\rightarrow6)$-D-glucosamine disaccharide substituted by phosphate groups and by ester- and amide-bound fatty acids[3] as indicated in Chart 1. Various lipid A analogs of a monosaccharide type have been synthesized, and among the synthetic analogs, D-glucosamine-4-phosphates as the nonreducing moiety of lipid A showed many of the biological activities of LPS.[4] As a synthetic approach to investigate the relationship between the chemical structure and the biological activity of the nonreducing subunit of lipid As, we describe in this paper a successful synthesis of D-galactosamine-4-phosphate derivatives (**1**) using a suitably functionalized key intermediate (**2**) carrying one amino and one hydroxyl group at the C-2 and C-3 positions of the D-galactosamine skeleton, respectively.

The key intermediate (**2**) was easily prepared starting from *N*-acetyl-D-galactosamine in 3 steps, as shown in Chart 2. The α-glycoside (**3**)[5] was converted into the 4-methoxybenzylidene derivative (**4**) with 4-methoxybenzaldehyde in the presence of anhydrous $ZnCl_2$ to give **4** in 73% yield. The nuclear magnetic resonance (^{1}H-NMR) spectrum of **4** showed the presence of the methoxy proton (CH_3O-) signal as a singlet at δ 3.81. Successful cleavage of the *N*-acetyl group of **4** was effected with KOH–EtOH at 110—120 °C[6] to afford the key intermediate (**2**) in 81% yield. The structure of **2** was confirmed by the disappearance of the acetyl proton (CH_3CO-) signal in the ^{1}H-NMR spectrum and the amide absorption in the infrared (IR) spectrum. The key intermediate (**2**) thus obtained was applied to the synthesis of the title compounds (**1**) as follows.

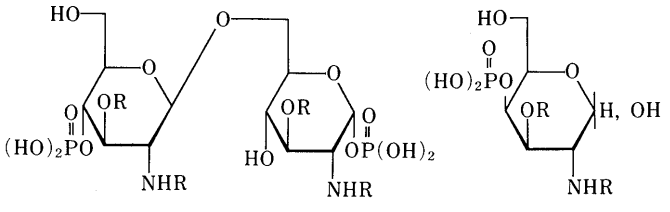
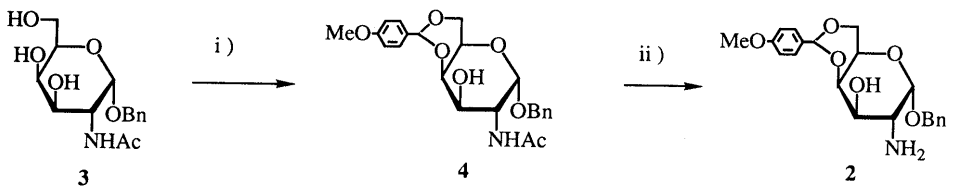


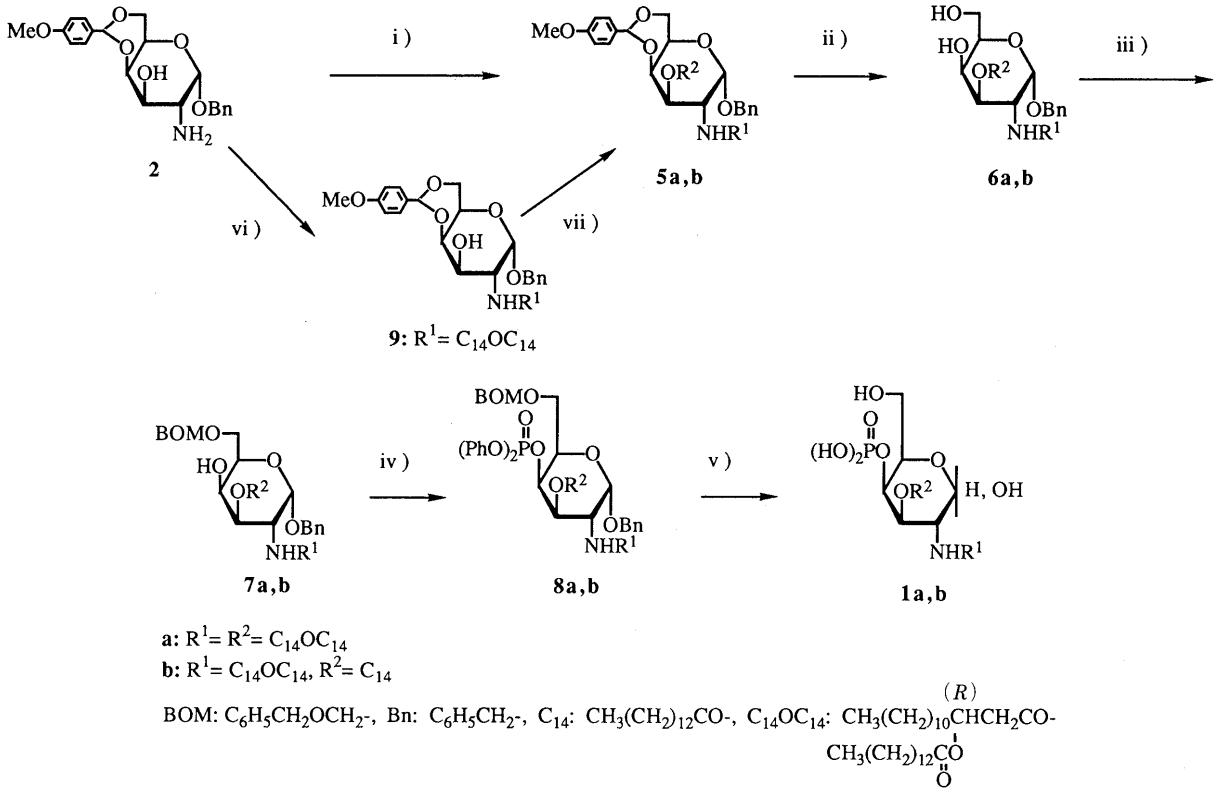
Chart 1

First, we selected the (*R*)-3-tetradecanoyloxytetradecanoyl group at *N*-2 and *O*-3 of the D-galactosamine backbone as the monosaccharide analogue of lipid A.[4c,d] The free amino and hydroxyl groups of **2** were simultaneously acylated with optically active (*R*)-3-tetradecanoyloxytetradecanoic acid in the presence of dicyclohexylcarbodiimide (DCC) and a catalytic amount of 4-dimethylaminopyridine (DMAP) in CH_2Cl_2 to give the diacylate (**5a**) in quantitative yield. Hydrolysis of the 4-methoxybenzylidene group of **5a** proceeded smoothly on treatment with 80% aqueous AcOH at 80—90 °C for 20 min, giving rise to the diol (**6a**) in 98% yield. In contrast, a preliminary experiment showed that the cleavage of the benzylidene group instead of the 4-methoxybenzylidene group of **5a** with aqueous AcOH gave compound (**6a**) only in poor yield (33% yield), together with decomposition products. The 6-*O*-hydroxyl group of **6a** was selectively protected with benzyloxymethyl chloride and tetramethylurea (TMU) in CH_2Cl_2 to give the benzyloxymethyl compound (**7a**) in 76% yield. Subsequent phosphorylation of **7a** with diphenylphosphoryl chloride in the presence of pyridine–DMAP in CH_2Cl_2 gave **8a** in 84% yield. Finally, the



reagents : i) 4-methoxybenzaldehyde, $ZnCl_2$, ii) KOH-EtOH

Chart 2



a: $R^1 = R^2 = C_{14}OC_{14}$
b: $R^1 = C_{14}OC_{14}$, $R^2 = C_{14}$

BOM: $C_6H_5CH_2OCH_2$-, Bn: $C_6H_5CH_2$-, C_{14}: $CH_3(CH_2)_{12}CO$-, $C_{14}OC_{14}$: $CH_3(CH_2)_{10}\overset{(R)}{C}HCH_2CO$-
$CH_3(CH_2)_{12}CO$

reagents: i) $C_{14}OC_{14}OH$, DCC, DMAP, ii) 80% AcOH, iii) benzyl chloromethyl ether, TMU
iv) diphenylphosphoryl chloride, DMAP, pyridine, v) Pd / C, H_2, then PtO_2, H_2
vi) $C_{14}OC_{14}OH$, DCC, vii) $C_{14}Cl$, DMAP, pyridine

Chart 3

protective benzyl and phenyl groups of **8a** were removed by stepwise hydrogenolysis catalyzed by 10% palladium on carbon at 45°C for 5 h and the platinum oxide at room temperature for 16 h in MeOH to afford the final product (**1a**) in 26% yield after purification on a silica gel column (CH_2Cl_2 : MeOH = 10 : 1) followed by lyophilization from dioxane.

Similarly, the compound (**1b**) bearing the (*R*)-3-tetradecanoyloxytetradecanoyl group at *N*-2 and the tetradecanoyl group at *O*-3 of the D-galactosamine skeleton of the GLA-27 type,[4e,h] was synthesized stepwise by successive acylation of the amino and hydroxyl groups of **2** under the same experimental conditions as applied to **1a**. The amino-hydroxyl compound (**2**) was first acylated at the amino group with (*R*)-3-tetradecanoyloxytetradecanoic acid and DCC in CH_2Cl_2 to give the monoacylate (**9**) in 88% yield. The remaining hydroxyl group of **9** was acylated with tetradecanoyl chloride, pyridine, and DMAP in CH_2Cl_2 to give the diacylate (**5b**) in 97% yield. Subsequently, cleavage of the 4-methoxybenzylidene group of **5b**, followed by selective benzyloxymethylation of the hydroxyl group at the C-6 position of **6b**, and the phosphorylation of the remaining hydroxyl group of **7b** led to **8b**. Finally, deprotection of **8b** as described for the preparation of **1a** gave the desired product (**1b**) in 82% yield. These compounds (**1a, b**) showed the characteristic blue color with the phosphate-specific spray reagent.[7] The structures of all compounds were characterized by ^{1}H-NMR and IR spectroscopies, and elemental analyses.

Preliminary examination of the biological activity[8] of the compounds (**1a, b**) showed that the chemically synthesized compounds (**1a, b**) possessed weaker mitogenic activity than that of the corresponding D-glucosamine-4-phosphate.

Experimental

All melting points are uncorrected. Optical rotations were measured with a JASCO DIP-140 digital polarimeter. IR spectra were recorded on a JASCO A-202 IR spectrophotometer ^{1}H-NMR spectra were taken on a JEOL JNM-GX 270 (270 MHz) spectrometer with tetramethylsilane (in $CDCl_3$) as an internal standard, and the chemical shifts are given in δ values. The abbreviations of signal patterns are as follows: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Column chromatography was carried out on Silica gel 60 (70—230 mesh, Merck). Thin-layer chromatography (TLC) on Silica gel 60-F_{254} (Merck) was used to monitor the reaction and to ascertain the purity of the reaction products. The spots were visualized by spraying the plates with 5% aqueous sulfuric acid and then heating.

Benzyl 2-Acetamido-2-deoxy-4,6-*O*-(4-methoxybenzylidene)-α-D-galactopyranoside (4) Anhydrous $ZnCl_2$ (1.0 g) was added to a stirred solution of compound **3** (1.1 g, 3.4 mmol) and 4-methoxybenzaldehyde (6.8 ml) at room temperature. After 15 h, the reaction mixture was poured into ice-cold water, then the precipitates were successively washed with *n*-pentane and ether, and dried *in vacuo* to give **4** (1.1 g, 73%), mp 179—182 °C. $[\alpha]_D^{20}$ +157° (c = 0.78, MeOH). IR (KBr) cm^{-1}: 1645, 1546 (amide), 687 (Ph). ^{1}H-NMR ($CDCl_3$) δ: 1.98 (3H, s, NAc), 3.68 (1H, br s, H-5), 3.81 (3H, s, OMe), 3.85 (1H, dd, $J_{2,3}$ = 11.5 Hz, $J_{3,4}$ = 3.5 Hz, H-3), 4.04 (1H, dd, $J_{6A,6B}$ = 12.5 Hz, $J_{6A,5}$ = 1.5 Hz, H-6_A), 4.21—4.23 (2H, m, H-4, H-6_B), 4.42 (1H, dd, $J_{1,2}$ = 3.5 Hz, $J_{2,3}$ = 11.5 Hz, H-2), 4.55, 4.73 (each 1H, d, J_{gem} = 11.5 Hz, OC$\underline{H}_2$Ph), 5.05 (1H, d, $J_{1,2}$ = 3.5 Hz, H-1), 5.54 (1H, s, *p*-MeOPhC$\underline{H}$), 6.89—7.48 (9H, m, Ph). *Anal.* Calcd for $C_{23}H_{27}NO_7 \cdot H_2O$: C, 61.73; H, 6.53; N, 3.13. Found: C, 61.99; H, 6.59; N, 3.38.

Benzyl 2-Amino-2-deoxy-4,6-*O*-(4-methoxybenzylidene)-α-D-galactopyranoside (2) A solution of compound **4** (1.1 g, 2.5 mmol) and KOH (4.0 g) in EtOH (13 ml) was heated at 110—120 °C for 7 h. After the mixture had cooled, an ion exchange resin IRC-50 (2.0 g) was added and the whole

was stirred for 1 h. The insoluble material was filtered off and the filtrate was concentrated to dryness *in vacuo*. The residue was subjected to silica gel chromatography with CH_2Cl_2–MeOH (5 : 1) to give **2** (0.78 g, 81%), mp 168 °C. $[\alpha]_D^{20}$ +133° (c=0.74, MeOH). IR (KBr) cm^{-1}: 3460 (OH), 3280 (NH_2), 718 (Ph). ^{1}H-NMR ($CDCl_3$) δ: 3.10 (1H, dd, $J_{1,2}$=3.2 Hz, $J_{2,3}$=10.3 Hz, H-2), 3.67 (1H, dd, $J_{4,5}$=4.0 Hz, $J_{5,6}$=1.6 Hz, H-5), 3.75 (1H, dd, $J_{2,3}$=10.3 Hz, $J_{3,4}$=3.5 Hz, H-3), 3.80 (3H, s, OMe), 4.03 (1H, dd, $J_{6A,6B}$=12.4 Hz, $J_{6A,5}$=1.6 Hz, H-6$_A$), 4.20 (1H, dd, $J_{3,4}$=3.5 Hz, $J_{4,5}$=4.0 Hz, H-4), 4.21 (1H, dd, $J_{6A,6B}$=12.4 Hz, $J_{6B,5}$=1.6 Hz, H-6$_B$), 4.58, 4.73 (each 1H, d, J_{gem}=11.7 Hz, OCH_2Ph), 5.08 (1H, d, $J_{1,2}$=3.2 Hz, H-1), 5.51 (1H, s, *p*-MeOPhC<u>H</u>), 6.87—7.44 (9H, m, Ph). *Anal.* Calcd for $C_{21}H_{25}NO_6$: C, 65.10; H, 6.50; N, 3.62. Found: C, 65.56; H, 6.54; N, 3.68.

Benzyl 2-Deoxy-4,6-*O*-(4-methoxybenzylidene)-2-[(*R*)-3-tetradecanoyloxytetradecanamido]-3-*O*-[(*R*)-3-tetradecanoyloxytetradecanoyl]-α-D-galactopyranoside (5a) DCC (0.17 g, 0.81 mmol) was added to a stirred solution of **2** (0.11 g, 0.27 mmol), (*R*)-3-tetradecanoyloxytetradecanoic acid (0.30 g, 0.65 mmol), and DMAP (33 mg, 0.27 mmol) in dry CH_2Cl_2 (2.5 ml) at 0 °C under argon. The mixture was stirred at 0 °C for 1 h, then at room temperature for 15 h. The resulting suspension was filtered through Celite 545 and evaporated. The residue was chromatographed on silica gel with CH_2Cl_2–acetone (50 : 1) to give **5a** (0.35 g, quantitative), mp 77—79 °C. $[\alpha]_D^{19}$ +90° (c=1.11, $CHCl_3$). IR (film) cm^{-1}: 1728 (ester), 1640, 1540 (amide), 682 (Ph). ^{1}H-NMR ($CDCl_3$) δ: 0.88 (12H, t, J=6.4 Hz, $(CH_2)_n$C<u>H</u>$_3$ × 4), 1.25 (84H, br s, $(CH_2)_n$), 3.80 (3H, s, OMe), 4.16—4.20 (3H, m, H-4, H-6$_A$ and H-6$_B$), 4.30—4.34 (1H, m, H-2), 4.54—4.77 (1H, m, H-3), 4.57, 4.72 (each 1H, d, J=11.9 Hz, OCH_2Ph), 5.07 (1H, d, $J_{1,2}$=3.7 Hz, H-1), 5.12—5.18 (2H, m, C<u>H</u>$(CH_2)_{10}CH_3$ × 2), 5.47 (1H, s, PhC<u>H</u>=), 6.76—7.45 (9H, m, Ph). *Anal.* Calcd for $C_{77}H_{129}NO_{12}$: C, 73.35; H, 10.31; N, 1.11. Found: C, 73.56; H, 10.19; N, 1.27.

Benzyl 2-Deoxy-2-[(*R*)-3-tetradecanoyloxytetradecanamido]-3-*O*-[(*R*)-3-tetradecanoyloxytetradecanoyl]-α-D-galactopyranoside (6a) A solution of **5a** (0.35 g, 0.28 mmol) in 80% aqueous AcOH (3.0 ml) was heated at 80—90 °C for 20 min. After removal of the solvent, the residue was chromatographed on silica gel with CH_2Cl_2–acetone (50 : 1) to give **6a** (0.32 g, 98%), mp 76—78 °C. $[\alpha]_D^{19}$ +55° (c=0.97, $CHCl_3$). IR (film) cm^{-1}: 3500 (OH), 3280 (NH), 1720 (ester), 1640, 1540 (amide), 686 (Ph). ^{1}H-NMR ($CDCl_3$) δ: 0.88 (12H, t, J=6.8 Hz, $(CH_2)_n$C<u>H</u>$_3$ × 4), 1.25 (84H, br s, $(CH_2)_n$), 2.18—2.60 (2H, m, H-6$_A$, H-6$_B$), 3.76—3.96 (3H, m, H-2, H-4, H-5), 4.51, 4.71 (each 1H, d, J=11.9 Hz, OCH_2Ph), 4.57—4.80 (1H, m, H-3), 5.03 (1H, d, $J_{1,2}$=3.7 Hz, H-1), 5.05—5.17 (2H, m, C<u>H</u>$(CH_2)_{10}CH_3$ × 2), 6.05 (1H, d, J=8.8 Hz, NH), 7.26—7.44 (5H, m, Ph). *Anal.* Calcd for $C_{69}H_{123}NO_{11}$: C, 72.52; H, 10.85; N, 1.23. Found: C, 72.16; H, 10.94; N, 1.34.

Benzyl 6-*O*-Benzyloxymethyl-2-deoxy-2-[(*R*)-3-tetradecanoyloxytetradecanamido]-3-*O*-[(*R*)-3-tetradecanoyloxytetradecanoyl]-α-D-galactopyranoside (7a) Benzyloxymethyl chloride (0.069 g, 0.44 mmol) was added to a stirred solution of **6a** (0.10 g, 0.087 mmol) and TMU (0.061 g, 0.52 mmol) in dry CH_2Cl_2 at 0 °C under argon. After 18 h at room temperature, the reaction mixture was successively washed with saturated $NaHCO_3$ and brine, and dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica gel with CH_2Cl_2–acetone (10 : 1) to give **7a** (0.084 g, 76%), mp 56—57 °C. $[\alpha]_D^{20}$ +41° (c=0.34, $CHCl_3$). IR (KBr) cm^{-1}: 3500 (OH), 3280 (NH), 1720 (ester), 1640, 1548 (amide), 696 (Ph). ^{1}H-NMR ($CDCl_3$) δ: 0.88 (12H, t, J=6.6 Hz, $(CH_2)_n$C<u>H</u>$_3$ × 4), 1.25 (84H, br s, $(CH_2)_n$), 3.74—3.85 (2H, m, H-2, H-5), 3.96—4.00 (1H, m, H-4), 4.50, 4.72 (each 1H, d, J=11.9 Hz, OCH_2Ph), 4.55—4.82 (3H, m, H-3, H-6$_A$, H-6$_B$), 4.61 (2H, s, OCH_2OCH_2Ph), 4.77 (2H, s, OCH_2OCH_2Ph), 5.00 (1H, d, $J_{1,2}$=4.0 Hz, H-1), 5.02—5.22 (2H, m, C<u>H</u>$(CH_2)_{10}CH_3$), 5.98 (1H, d, J=9.2 Hz, NH), 7.26—7.37 (10H, m, Ph). *Anal.* Calcd for $C_{77}H_{131}NO_{12}\cdot H_2O$: C, 72.20; H, 10.49; N, 1.09. Found: C, 72.21; H, 10.90; N, 1.56.

Benzyl 6-*O*-Benzyloxymethyl-2-deoxy-4-*O*-diphenylphosphoryl-2-[(*R*)-3-tetradecanoyloxytetradecanamido]-3-*O*-[(*R*)-3-tetradecanoyloxytetradecanoyl]-α-D-galactopyranoside (8a) Diphenylphosphorochloridate (0.034 g, 0.13 mmol) was added to a stirred solution of **7a** (0.060 g, 0.047 mmol), pyridine (0.019 g, 0.24 mmol) and DMAP (0.029 g, 0.24 mmol) at 0 °C under argon, and then the mixture was stirred for 15 h at room temperature. The reaction mixture was washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, and evaporated. The residue was chromatographed on silica gel with CH_2Cl_2 to give **8a** (0.060 g, 84%), syrup. $[\alpha]_D^{24}$ +23° (c=1.10, $CHCl_3$). IR (film) cm^{-1}: 3272 (NH), 1720 (ester), 1637, 1541 (amide), 950 (POPh), 680 (Ph). ^{1}H-NMR ($CDCl_3$) δ: 0.88 (12H, t, J=6.6 Hz, $(CH_2)_n$C<u>H</u>$_3$ × 4), 1.25 (84H, br s, $(CH_2)_n$), 3.74—3.88 (2H, m, H-2, H-5), 4.50, 4.73 (each 1H, d, J=12.1 Hz, =CHOC<u>H</u>$_2$Ph), 4.56—4.81 (3H, m, H-3, H-6$_A$, H-6$_B$), 4.61 (2H, s, $PhCH_2OC\underline{H}_2O$), 4.77 (2H, s, $PhC\underline{H}_2OCH_2O$), 5.00 (1H, d, $J_{1,2}$=3.7 Hz, H-1), 5.03—5.28 (2H, m, C<u>H</u>$(CH_2)_{10}CH_3$ × 2), 6.03 (1H, d, J=9.2 Hz, NH), 7.16—7.38 (20H, m, Ph). *Anal.* Calcd for $C_{89}H_{140}NO_{15}P$: C, 71.50; H, 9.44; N, 0.94. Found: C, 71.10; H, 10.03; N, 0.96.

2-Deoxy-4-*O*-phosphono-2-[(*R*)-3-tetradecanoyloxytetradecanamido]-3-*O*-[(*R*)-3-tetradecanoyloxytetradecanoyl]-D-galactopyranose (1a) Compound **8a** (0.060 g, 0.04 mmol) in MeOH (2.0 ml) was hydrogenated in the presence of 10% Pd-on-carbon (20 mg) at room temperature for 5 h. The catalyst was filtered off and Adams' platinum catalyst (15 mg) was added to the filtrate. Hydrogenolysis was continued at room temperature for 18 h. The catalyst was filtered off and the filtrate was evaporated to give an oil, which was subjected to preparative TLC (CH_2Cl_2 : acetone = 10 : 1) to give **1a** (12 mg, 26%), mp 41—42 °C. $[\alpha]_D^{21}$ +36° (c=0.13, $CHCl_3$: MeOH = 1 : 1). IR (film) cm^{-1}: 3420 (OH), 3280 (NH), 1724 (ester), 1648, 1540 (amide), 1167 (POH). ^{1}H-NMR ($CDCl_3$) δ: 0.88 (12H, t, J=7.0 Hz, $(CH_2)_n$C<u>H</u>$_3$), 1.26 (84H, br s, $(CH_2)_n$), 4.86 (1H, d, $J_{1,2}$=3.3 Hz, H-1), 5.04—5.23 (2H, m, C<u>H</u>(CH_2)), 5.92 (1H, d, J=9.2 Hz, NH). Positive ion FAB-mass spectrometry (triethanolamine), m/z: 1333 (M + H)$^+$.

Benzyl 2-Deoxy-4,6-*O*-(4-methoxybenzylidene)-2-[(*R*)-3-tetradecanoyloxytetradecanamido]-α-D-galactopyranoside (9) DCC (0.19 g, 0.90 mmol) was added to a stirred solution of **2** (0.21 g, 0.60 mmol) and (*R*)-3-tetradecanoyloxytetradecanoic acid (0.33 g, 0.72 mmol) in dry CH_2Cl_2 (10 ml) at 0 °C under argon. The mixture was stirred at 0 °C for 1 h, and then at room temperature for 15 h. The resulting suspension was filtered through Celite 545 and evaporated. The residue was chromatographed on silica gel with CH_2Cl_2–acetone (50 : 1) to give **9** (0.42 g, 88%), mp 141—144 °C. $[\alpha]_D^{19}$ +77° (c=0.16, $CHCl_3$). IR (film): 3515 (OH), 1720 (ester), 1640, 1540 (amide), 685 cm^{-1} (Ph). ^{1}H-NMR ($CDCl_3$) δ: 0.88 (12H, t, J=6.4 Hz, $(CH_2)_n$C<u>H</u>$_3$ × 2), 1.25 (42H, br s, $(CH_2)_n$), 3.81 (3H, s, OMe), 4.56, 4.73 (each 1H, d, J=12.1 Hz, $OC\underline{H}_2Ph$), 5.04 (1H, d, $J_{1,2}$=3.3 Hz, H-1), 5.22 (1H, m, C<u>H</u>$(CH_2)_{10}CH_3$ × 2), 5.52 (1H, s, MeOPhC<u>H</u>), 5.97 (1H, d, J=9.2 Hz, NH), 6.87—7.45 (9H, m, Ph). *Anal.* Calcd for $C_{49}H_{77}NO_9\cdot H_2O$: C, 69.88; H, 9.46; N, 1.66. Found: C, 69.45; H, 9.37; N, 2.25.

Benzyl 2-Deoxy-4,6-*O*-(4-methoxybenzylidene)-3-*O*-tetradecanoyl-2-[(*R*)-3-tetradecanoyloxytetradecanamido]-α-D-galactopyranoside (5b) Tetradecanoyl chloride (0.16 g, 0.64 mmol) was added to a stirred solution of **9** (0.42 g, 0.53 mmol), pyridine (0.063 g, 0.8 mmol), and DMAP (0.033 g, 0.27 mmol) in dry CH_2Cl_2 (10 ml) at 0 °C under argon. The mixture was stirred for 1 h, then at room temperature for 15 h. The resulting mixture was washed with saturated aqueous $NaHCO_3$, and brine. The organic layer was dried over anhydrous $MgSO_4$ and evaporated to dryness. The residue was purified on a column of silica gel (CH_2Cl_2 : isopropyl ether (IPE) = 50 : 1) to give **5b** (0.53 g, 97%), mp 101—102 °C. $[\alpha]_D^{20}$ +90° (c=0.30, $CHCl_3$). IR (film) cm^{-1}: 1728 (ester), 1646, 1552 (amide), 685 (Ph). ^{1}H-NMR ($CDCl_3$) δ: 0.88 (9H, t, J=7.0 Hz, $(CH_2)_n$C<u>H</u>$_3$), 1.26 (64H, br s, $(CH_2)_n$), 3.81 (3H, s, OMe), 4.01—4.21 (2H, m, H-6), 4.56, 4.72 (each 1H, d, J=12.1 Hz, $OC\underline{H}_2Ph$), 5.08 (1H, d, $J_{1,2}$=3.7 Hz, H-1), 5.19—5.22 (1H, m, C<u>H</u>$(CH_2)_n$), 5.49 (1H, s, MeOPhC<u>H</u>), 5.88 (1H, d, J=9.5 Hz, NH), 6.86—7.45 (9H, m, Ph). *Anal.* Calcd for $C_{63}H_{103}NO_{10}\cdot H_2O$: C, 71.94; H, 10.23; N, 1.33. Found: C, 71.42; H, 9.96; N, 1.40.

Benzyl 2-Deoxy-3-*O*-tetradecanoyl-2-[(*R*)-3-tetradecanoyloxytetradecanamido]-α-D-galactopyranoside (6b) Compound **6b** was obtained from **5b** by a procedure similar to that described for **6a** and was chromatographed on silica gel with CH_2Cl_2–acetone (10 : 1) to give **6b**; 72% yield, mp 114—117 °C. $[\alpha]_D^{23}$ +64° (c=0.40, $CHCl_3$). IR (film) cm^{-1}: 3485 (OH), 3280 (NH), 1717 (ester), 1635, 1550 (amide), 685 (Ph). ^{1}H-NMR ($CDCl_3$) δ: 0.88 (9H, t, J=6.6 Hz, $(CH_2)_n$C<u>H</u>$_3$ × 3), 1.25 (64H, br s, $(CH_2)_n$), 3.89—4.04 (3H, m, H-2, H-4, H-5), 4.52, 4.72 (each 1H, d, J=11.9 Hz, $OC\underline{H}_2Ph$), 4.57—4.74 (1H, m, H-3), 4.98 (1H, d, $J_{1,2}$=3.7 Hz, H-1), 5.13—5.18 (2H, m, C<u>H</u>$(CH_2)_{10}CH_3$ × 2), 5.88 (1H, d, J=9.5 Hz, NH), 7.26—7.34 (5H, m, Ph). *Anal.* Calcd for $C_{55}H_{97}NO_9\cdot H_2O$: C, 70.70; H, 10.68; N, 1.50. Found: C, 71.10; H, 10.90; N, 1.82.

Benzyl 6-*O*-Benzyloxymethyl-2-deoxy-3-*O*-tetradecanoyl-2-[(*R*)-3-tetradecanoyloxytetradecanamido]-α-D-galactopyranoside (7b) Compound **7b** was obtained from **6b** by a procedure similar to that described for **7a** and was chromatographed on silica gel with CH_2Cl_2–acetone (10 : 1); 59% yield, mp 88—89 °C. $[\alpha]_D^{23}$ +57° (c=0.43, $CHCl_3$). IR (KBr) cm^{-1}: 3500 (OH), 3280 (NH), 1713 (ester), 1635, 1550 (amide), 695 (Ph). ^{1}H-NMR ($CDCl_3$) δ: 0.88 (9H, t, J=6.6 Hz, $(CH_2)_n$C<u>H</u>$_3$ × 3), 1.25 (64H, br s, $(CH_2)_n$), 3.75—3.86 (2H, m, H-2, H-5), 3.98—4.02 (1H, m, H-4), 4.50, 4.72 (each 1H, d, J=11.7 Hz, $OC\underline{H}_2Ph$), 4.55—4.81 (3H, m, H-3, H-6$_A$, H-6$_B$), 4.61 (2H, s, $OCH_2OC\underline{H}_2Ph$), 4.78 (2H, s, $OC\underline{H}_2OCH_2Ph$), 4.95 (1H, d, $J_{1,2}$=3.7 Hz, H-1), 5.05—5.17 (2H, m, C<u>H</u>$(CH_2)_{10}CH_3$), 5.85 (1H, d, J=9.5 Hz, NH), 7.26—7.36 (10H, m, Ph). *Anal.* Calcd for

$C_{63}H_{105}NO_{10}$: C, 73.00; H, 10.21; N, 1.35. Found: C, 72.48; H, 10.49; N, 1.27.

Benzyl 6-*O*-Benzyloxymethyl-2-deoxy-4-*O*-diphenylphosphoryl-3-*O*-tetradecanoyl-2-[(*R*)-3-tetradecanoyloxytetradecanamido]-α-D-galactopyranoside (8b) Compound **8b** was obtained from **7b** by a procedure similar to that described for **8a** and was chromatographed on silica gel with CH_2Cl_2 to give **8b**; 87% yield, syrup. $[\alpha]_D^{20}$ +40° (c=0.74, $CHCl_3$). IR (film) cm^{-1}: 1733 (ester), 1648, 1536 (amide), 950 (POPh), 680 (Ph). ^{1}H-NMR ($CDCl_3$) δ: 0.88 (9H, t, J=6.6 Hz, $(CH_2)_n$ CH_3 ×3), 1.25 (64H, br s, $(CH_2)_n$), 4.50, 4.73 (each 1H, d, J=11.7 Hz, $CHOCH_2Ph$), 4.96 (1H, d, $J_{1,2}$=3.7 Hz, H-1), 5.00—5.26 (2H, m, $CH(CH_2)_{10}CH_3$ ×2), 5.81 (1H, d, J=9.2 Hz, NH), 7.19—7.38 (20H, m, Ph). *Anal.* Calcd for $C_{75}H_{104}NO_{13}P \cdot 2H_2O$: C, 69.58; H, 8.41; N, 1.08. Found: C, 69.29; H, 8.72; N, 1.06.

2-Deoxy-4-*O*-phosphono-3-*O*-tetradecanoyl-2-[(*R*)-3-tetradecanoyloxytetradecanamido]-D-galactopyranose (1b) Compound **1b** was obtained from **8b** by a procedure similar to that described for **1a** and was chromatographed on silica gel with CH_2Cl_2–MeOH (10:1) to give **1b**; 69% yield, syrup. $[\alpha]_D^{20}$ +32° (c=1.16, $CHCl_3$). IR (film) cm^{-1}: 3430 (OH), 3280 (NH), 1735 (ester), 1665, 1546 (amido), 1160 (POH). ^{1}H-NMR ($CDCl_3$) δ: 0.88 (9H, t, J=7.0 Hz, $(CH_2)_nCH_3$), 1.26 (64H, br s, $(CH_2)_n$). *Anal.* Calcd for $C_{48}H_{82}NO_{12}P \cdot 3H_2O$: C, 60.67; H, 9.33; N, 1.47. Found: C, 60.17; H, 9.09; N, 1.82.

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